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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/838,987	Chamberlain et al.
Examiner	**Art Unit**
Michael C. Wilson	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 10, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 21, and 22* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 21, and 22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-10-03, paper number 10, has been entered.

The amendment to pg 1, line 3, in the amendment filed 2-10-03, paper number 11, has not been entered. The paragraph cannot be "replaced" as requested because a paragraph describing the priority information does not exist.

Applicant's arguments filed 2-10-03, paper number 11, have been fully considered but they are not persuasive. Claims 9-20 have been canceled. Claims 21 and 22 have been added. Claims 1-8, 21 and 22 are pending in the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

1. The amendment filed 2-10-03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The description of Fig. 1 contains new matter. The phrase "tumor growth", "The mice were primed with various vectors 3 days post-intravenous challenge" and "array of vectors" cannot be found in the specification as originally filed. Support for the rest of the description can be found on pg 21, line 6, pg 22, line 2 or is readily apparent in Fig. 1A-E. Applicant is required to cancel the new matter in the reply to this Office Action.

The heading describing Fig. 1 should begin --Fig. 1A-1E--.

Claim Rejections - 35 USC § 112

2. Claims 1-8 remain rejected and claims 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a CTL response in a mammal comprising administering a vaccinia viral vector encoding an antigen operably linked to a promoter followed by administering a fowlpox vector encoding said antigen operably linked to a promoter such that a CTL response against said antigen occurs as compared to vaccinia followed by vaccinia, fowlpox followed by fowlpox or fowlpox followed by vaccinia,

does not reasonably provide enablement for obtaining an immune response using any combination of vectors as broadly claimed or inducing a therapeutic or prophylactic immune response against an antigen using the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The claims are not enabled because merely inducing "an immune against at least one antigen" in context of the specification does not have a use without obtaining a therapeutic or prophylactic immune response. The specification teaches obtaining immune responses using the claimed invention that do not treat or prevent disease (e.g. vectors encoding β-gal). The only disclosed purpose for obtaining an immune response against β-gal is for further study to find methods of vaccination that generate a CTL or antibody response that is therapeutic or prophylactic (pg 4, lines 2-13). It was known in the art that a CTL response against β-gal could be induced upon administering wild-type vaccinia followed by a fowlpox vector encoding β-gal (Wang, 1995, J. Immunol., Vol. 154, pages 4685-4692). Administering wild-type fowlpox followed by vaccinia virus encoding β-gal also provided a CTL response against β-gal (pg 4689, col. 2, last sentence).

It was also known in the art at the time of filing that the combination of vector, promoter, antigen, target tissue, level of expression and route of administration required to target the desired tissue and obtain a therapeutic or prophylactic effect using gene therapy was unpredictable (Miller, 1995, FASEB J., Vol. 9, pages 190-199; pg 198, col. 1; Deonarain, 1998,

Expert Opin. Ther. Pat., Vol. 8, pages 53-69; pg 53, first para., pg 65, first para. under Conclusion; Verma, Sept. 1997, Nature, Vol. 389, pages 239-242; see entire article, pg 240, sentence bridging col. 2-3; Crystal, 1995, Science, Vol. 270, pg 404-410; pg 409, all of record).

The specification demonstrates administering a vaccinia, fowlpox or plasmid vector encoding β-gal followed by a different boosting vector encoding β-gal and obtaining a CTL response against β-gal as compared to vaccinia followed by vaccinia or fowlpox followed by fowlpox (page 25, Ex. 2). The specification discusses various viral vectors (pg 9-10) and various antigens (pg 11-13) to treat a variety of diseases including cancer (pg 11, lines 11-35). Example 1 teaches increasing survival of mice having β-gal-expressing tumors using vaccinia followed by fowlpox or fowlpox followed by vaccinia, each of which encode β-gal (page 21; Fig.1) and contemplates administering vectors encoding tumor associated antigens (TAA) against melanoma (example 5). The specification does not provide adequate guidance to treat cancer as claimed because the β-gal tumors do not correlate to tumors having tumor associated antigens. β-gal does not correlate to any TAA because it is a foreign protein while TAAs are self-proteins, because β-gal and TAAs known in the art do not have the same epitopes recognized by the immune system, β-gal and TAA have different MHC restriction and because β-gal and TAAs ability to induce immunity differ. Specifically, the specification does not provide any guidance to treat cancer using MART-1, gp100, TRP-1 or TRP-2 because the specification does not correlate the epitope of β-gal is the same amino acid sequence and structure as epitopes of

MART-1, gp100, TRP-1 or TRP-2, that MART-1, gp100, TRP-1 or TRP-2 are H-2L^d -restricted, or that MART-1, gp100, TRP-1 or TRP-2 induce an equivalent immune response as β-gal.

Thus, the specification does not provide adequate guidance for one of skill to administer a vector to a mammal to obtain a therapeutic or prophylactic immune response against an antigen by teaching the level of expression of antigen required to induce the desired immune response, how to target antigen expression to the desired tissue such that the desired immune response is obtained, or by correlating β-gal to tumor antigens such as MART-1, gp100, TRP-1 or TRP-2. Given the state of the art at the time of filing taken with the teachings in the specification, it would require one of skill undue experimentation to determine the dosage, route of administration, vector, promoter, antigens, target tissue or level of antigen expression required to obtain a therapeutic or prophylactic immune response using the claimed invention.

Applicants argue pg 7, line 5, , pg 9, pg 21, pg 11, line 4, pg 13, 19, pg 16, line 6, and pg 17, line 2, teaches any vector can be used in the instant invention with numerous antigens, immunostimulatory molecules, dosages and routes of administration to obtain an immune response that is therapeutic. Applicants argument is not persuasive. The specification does not enable treating or preventing disease because tumors expressing β-gal do not correlate to tumors expressing tumor antigens. The specification does not overcome the art established unpredictability of gene therapy established by Miller, Deonarain, Verma, and Crystal, all of record by teaching the specific combination of parameters required to use the instant invention to obtain a therapeutic or prophylactic immune response. It would have required one of skill undue

experimentation to determine how to use the lists of possible vectors, antigens, dosages and routes of administration to treat or prevent disease.

Applicants argue pg 4, lines 2-13, and pg 18, lines 26-33 teach using the injection strategy claimed to treat cancer, infectious disease, autoimmune disease, or fungus or virus-related disease. Applicants argument is not persuasive because the specification does not overcome the unpredictability in the art by teaching the specific parameters required to use the invention to treat disease. Pg 18, lines 26-33, does not teach the immune response obtained treated or prevented influenza.

3. Claims 1-8 remain rejected and claims 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The rejections regarding the phrases "heterologous boosting immunization," "DNA [or viral] vector and a nucleic acid encoding said antigen," "antigen-associated disease" and "immunostimulatory molecule" have been withdrawn because the phrase has been deleted.

Claim 1 is indefinite because it does not clearly set forth that the inserts of the first and second vectors encode the same antigen. The phrase "wherein at least one antigen encoded by the insert..." does not refer to "the at least one antigen" encoded by the insert. Thus, it cannot be determined whether the inserts of the first and second vectors encode the same antigen. The phrase --a second recombinant vector comprising a nucleic acid insert encoding said at least one antigen against which an immune response is to be induced-- and deleting "wherein at least one

antigen encoded by the insert of the first recombinant vector is encoded by the insert of the second recombinant vector," would overcome this rejection.

Claim 1 remains indefinite because it is not clear that the immune response induced is directed toward the antigen encoded by the vectors. The phrase --whereupon an immune response against said at least one antigen is induced in the mammal-- would overcome this rejection.

Claim 5 as newly amended is rejected because it does not clearly set forth the structure of the insert. It is unclear if the "antigen against which an immune response is to be induced" is limited to the "at least one antigen" encoded by the first and second vector in claim 1 or encompasses any antigen.

Claims 21 and 22 are indefinite because it is unclear if the "antigen against which an immune response is to be induced" refers to the "at least one antigen" encoded by the first and second vector in claim 1 or to a second antigen encoded by the vectors.

Claim Rejections - 35 USC § 103

4. Claims 1-3 and 5-7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92) for reasons of record.

Wang taught administering a wild-type vaccinia virus to mice followed by administering a fowlpox virus encoding β-gal which caused an increase in CTL response in splenocytes as compared to administering wild-type vaccinia followed by vaccinia encoding β-gal (page 4689,

col. 2, Fig. 6, 1st full para.). The increased CTL response is "an immune response" against the "at least one antigen" as claimed. Wang did not teach administering vaccinia virus encoding β-gal followed by administering fowlpox virus encoding β-gal. However, Wang taught a vaccinia virus encoding β-gal. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to pre-immunize with vaccinia encoding β-gal followed by fowlpox encoding β-gal as taught by Wang. One of ordinary skill in the art at the time the invention was made would have been motivated to replace wild-type vaccinia with vaccinia encoding β-gal to introduce the DNA encoding the antigen sooner while pre-immunizing.

Similarly, Wang taught administering a wild-type fowlpox followed by vaccinia encoding β-gal which also caused an immune response (page 4689, col. 2, 1st para.). Wang did not teach pre-immunizing with fowlpox encoding β-gal followed by vaccinia encoding β-gal. However, Wang taught administering fowlpox virus encoding β-gal caused an immune response. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to pre-immunize with fowlpox encoding β-gal followed by vaccinia encoding β-gal. One of ordinary skill in the art at the time the invention was made to replace wild-type fowlpox with fowlpox encoding β-gal to introduce the DNA encoding the antigen sooner while pre-immunizing.

Claim 5 is included because vaccinia and fowlpox virus encodes viral proteins which are recognized as foreign and induce an immune response.

Applicants argue Wang did not teach inducing an immune response (pg 6, 6 lines from the bottom, of the response). Applicants' argument is not persuasive because an increased CTL response against β-gal is "inducing an immune response" as claimed. FPV did not suppress the anti-β-gal response (pg 4689, col. 2, 1st para.).

Applicants argue there is not teaching or suggestion to inoculate in the manner taught by the present invention, with different vectors encoding the same antigen. Applicants argument is not persuasive. The reference need not specifically teach or suggest inoculating with different vectors each of which encodes the same antigen. One of ordinary skill in the art at the time the invention was made would have been motivated to replace wild-type vaccinia (administered before FPV encoding β-gal) with vaccinia encoding β-gal to introduce the DNA encoding the antigen sooner in a pre-immunization. One of ordinary skill in the art at the time the invention was made to replace wild-type fowlpox (administered before VV encoding β-gal) with fowlpox encoding β-gal to introduce the DNA encoding the antigen sooner during pre-immunization.

5. Claims 1-3 and 5-7 remain rejected and claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92) for reasons of record.

Wang taught administering vaccinia encoding β-gal to mice followed by administering fowlpox encoding β-gal or vice versa which caused an immune response (see 103 rejection above). Wang did not expressly teach performing the method wherein β-gal is replaced with MART-1 or gp100. However, Wang suggested replacing β-gal with MART-1 and gp100 and

taught making fowlpox virus encoding MART-1 and gp100 (page 4690, col. 2, last 2 para.). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein the β-gal gene is replaced with MART-1 or gp100 as suggested by Wang. One of ordinary skill in the art at the time the invention was made would have been motivated to replace β-gal with MART-1 or gp100 to determine if self proteins such as MART-1 or gp100 induced the same immune response as a foreign protein (β-gal) and to determine if MART-1 or gp100 enhanced the precursor frequency of T-cells that recognize MART-1 or gp100 prior to *ex vivo* expansion (page 4690, col. 2, para. 2, line 4).

Claim 5 is included because vaccinia and fowlpox virus encodes viral proteins which are recognized as foreign and induce an immune response.

Applicants have not argued this rejection.

The rejection of claims 1-3 and 5-7 under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92) in view of Orlow (1995, PNAS, Vol. 92, pages 10152-10156) has been withdrawn because claims directed toward TRP-1 or TRP-2 have been canceled (claims 12 and 13).

6. Claim 1-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92) in view of Zhai (Jan. 15, 1996, J. Immunol., Vol. 156, No. 2, pages 700-710) for reasons of record.

Wang taught administering a vaccinia virus encoding β-gal to a mice followed by administering a fowlpox virus encoding β-gal which caused an increase in CTL response in

splenocytes as compared to administering two doses of vaccinia virus encoding β-gal. Wang did not teach replacing the vaccinia virus or fowlpox virus with an adenovirus. However, Zhai taught administering an adenoviral vector encoding β-gal to mice and obtaining an immune response.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein the vaccinia virus or fowlpox virus was replaced with the adenoviral vector taught by Zhai. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the vaccinia virus (the first vector) with the adenoviral vector to increase the CTL response against antigen as compared to administering adenoviral vector followed by readministration of adenoviral vector. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the fowlpox virus (the second vector) with the adenoviral vector to determine if fowlpox was the only virus that could be used to obtain a CTL response against antigen after administering vaccinia virus.

Applicants teach the deficiencies of Wang and Zhai but do not provide any specific arguments regarding why the combined teachings of Wang and Zhai do not teach all the limitations of the claims or why motivation is lacking (pg 8 of response). Therefore, applicants argument is not persuasive because the combined teachings of Wang and Zhai taught all the limitations of claim and because one of ordinary skill in the art would have been motivated to combine the teachings of Wang and Zhai.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson